第42章

AGENTS THAT AFFECT BONE MINERAL HOMEOSTASIS

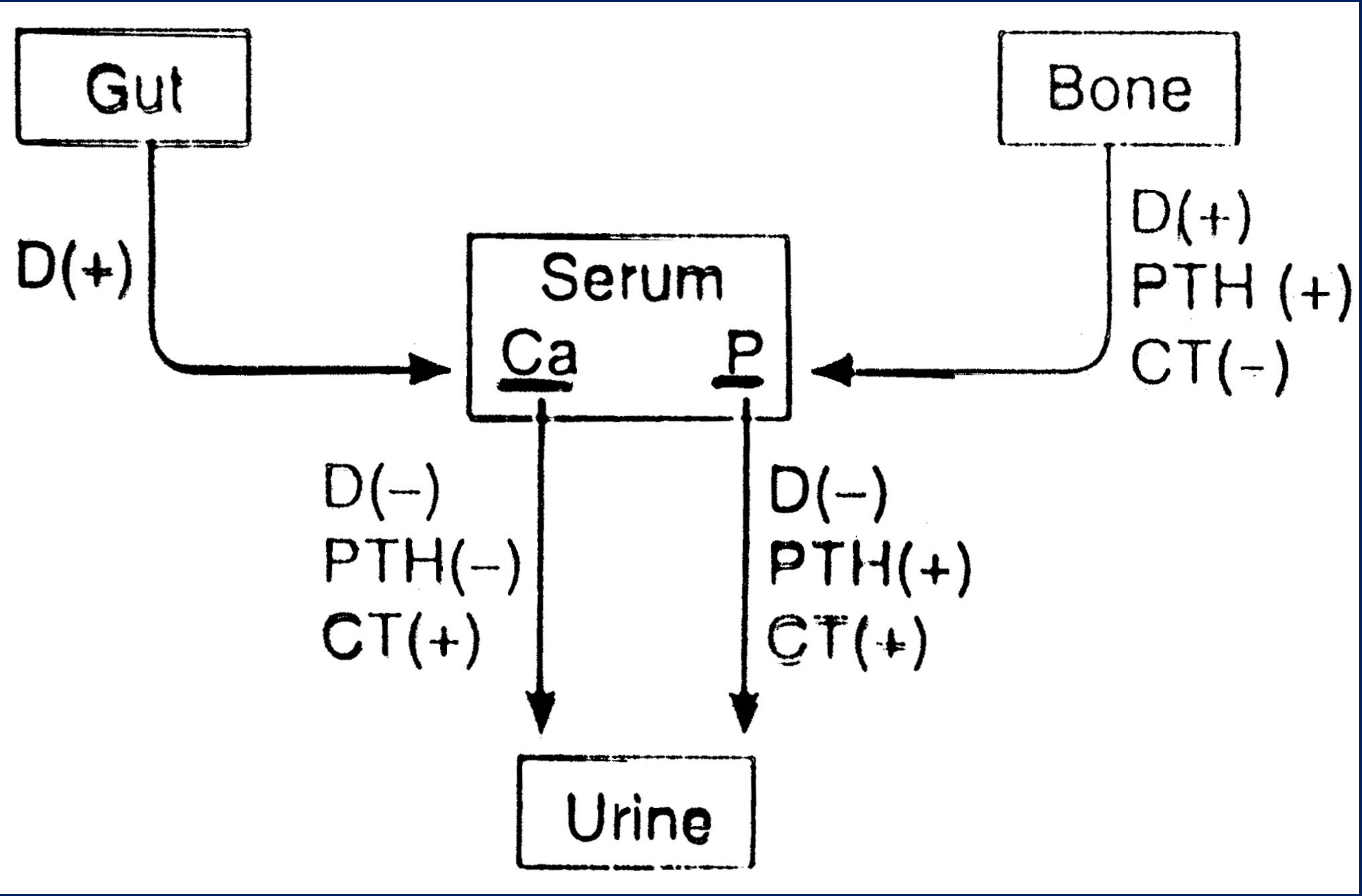
I. BASIC PHARMACOLOGY

→骨內主要之礦物質為calcium 與 phospate

→calcium 與 phosthate 主要由腸胃道吸收

→調節 calcium 與 phosphate homeostasis 之 hormone為:

- 1. polypeptide parathyroid hormons (PTH)
- 2. steroid vitamin D
- 3. others: calcitonin, prolactin, growth hormone, insulin, thyroid hormone, glucocorticoids and sex steroid .



Gut
Bone
D(+)
D(+)
PTH (+)
CT(–)
Serum
Ca
P
D(–)
PTH(–)
CT(+)
D(–)
PTH(+)
CT(+)
Urine

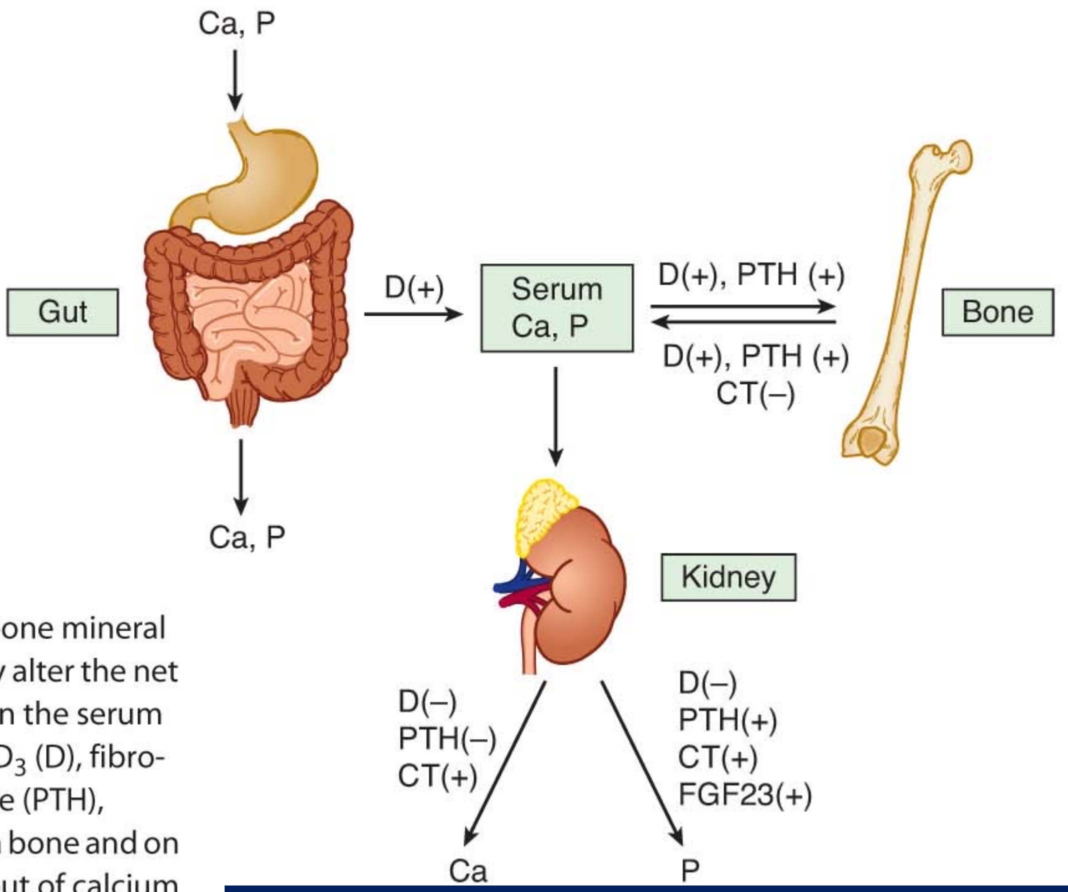


FIGURE 42–1 Some mechanisms contributing to bone mineral homeostasis. Direct actions are shown and feedback may alter the net effect. Calcium (Ca) and phosphorus (P) concentrations in the serum are controlled principally by three hormones, 1,25$(OH)_2D_3$ (D), fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on excretion in the urine. PTH and 1,25$(OH)_2D_3$ increase input of calcium and phosphorus from bone into the serum and stimulate bone formation. 1,25$(OH)_2D_3$ also increases calcium and phosphate absorption from the gut. 1,25$(OH)_2D_3$ decreases urinary excretion of both calcium and phosphorus, whereas PTH reduces calcium but increases phosphorus excretion. FGF23 stimulates renal excretion of phosphate. Calcitonin (CT) is a less critical hormone for calcium homeostasis, but in pharmacologic concentrations can reduce serum calcium and phosphorus by inhibiting bone resorption and stimulating their renal excretion. Feedback may alter the effects shown; for example, vitamin D usually increases urinary calcium excretion because of effects on calcium absorption from the gut and effects on PTH.

	PTH	Vit D
小腸	增加鈣、磷吸收↑	增加鈣、磷吸收
腎	減少鈣排泄↓ 增加磷排泄↑	減少鈣、磷排泄
骨	於高劑量增加鈣、磷吸收於低劑量增加骨骼形成	增加鈣、磷吸收
血中淨值	鈣↑ 磷↓	鈣↑ 磷↑

Principal Hormonal Regulators of Bone Mineral Homeostasis

一、Parathyroid Hormone

※ 骨、 礦物質平衡之主要荷爾蒙調節劑:

<1>.PTH : 84 氨基酸 ， 刺激 1,25$(OH)_2$D 形成

<2>.Vit D : 為prohormone， 接受紫外光，由皮膚製造。

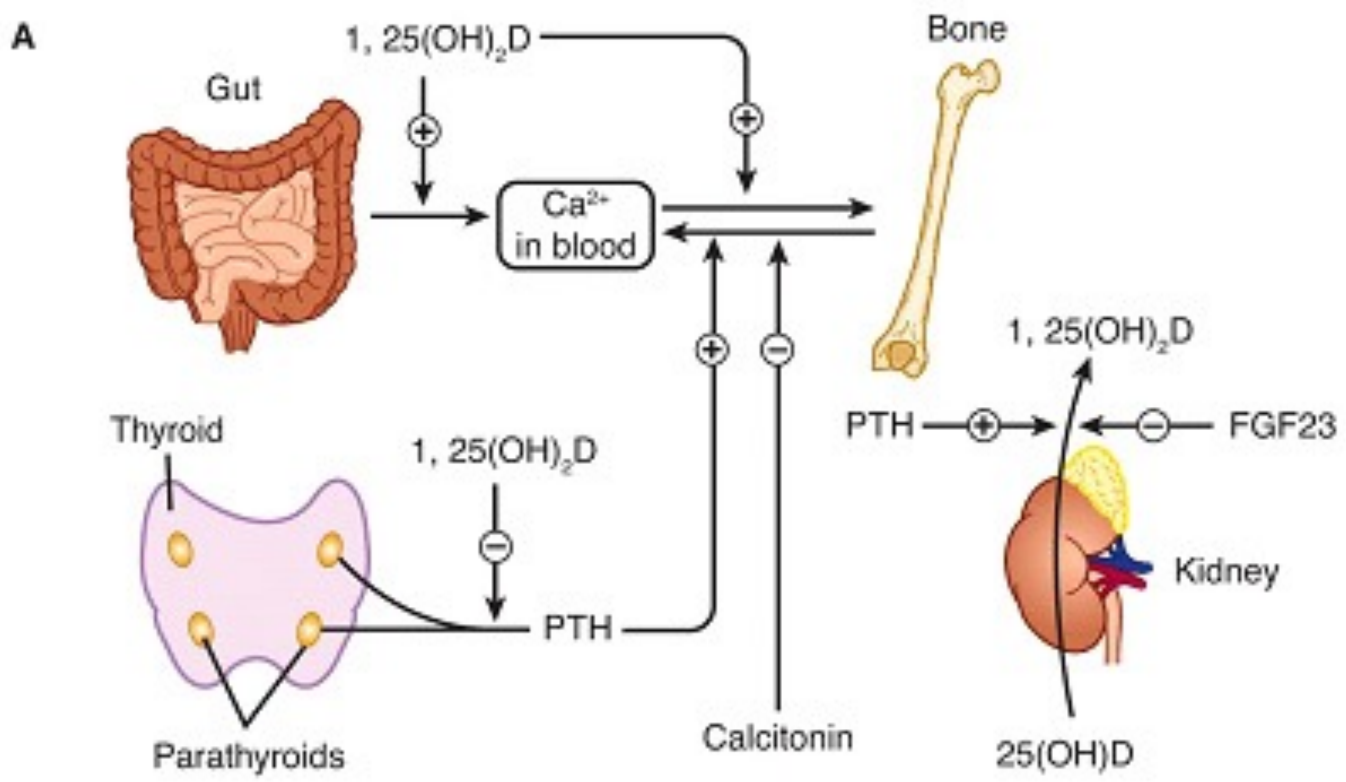
二、Vit D

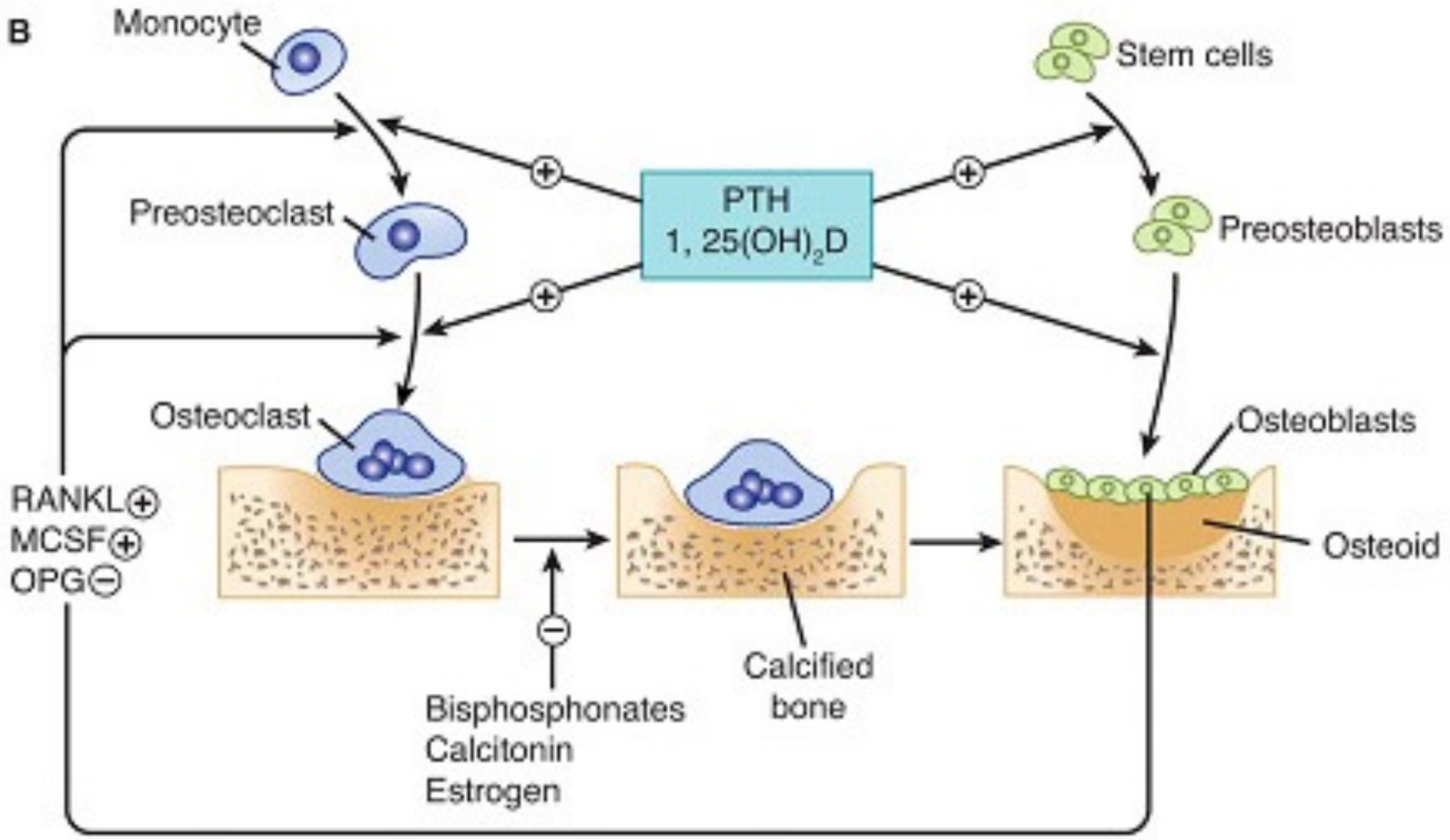
Vit D_2 (Ergocalciferol) → 經肝 hydroxylate 才有效。

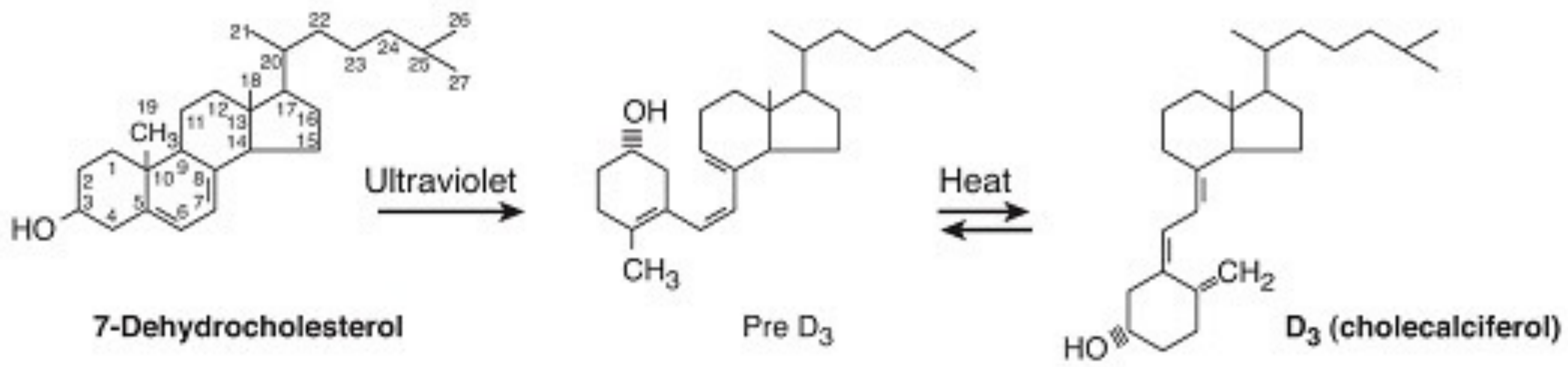
Vit D_3 (Cholecalciferol)→ 經肝 hydroxylate才有效。

※臨床上常用 : 25(OH) D_3 : Calcifediol

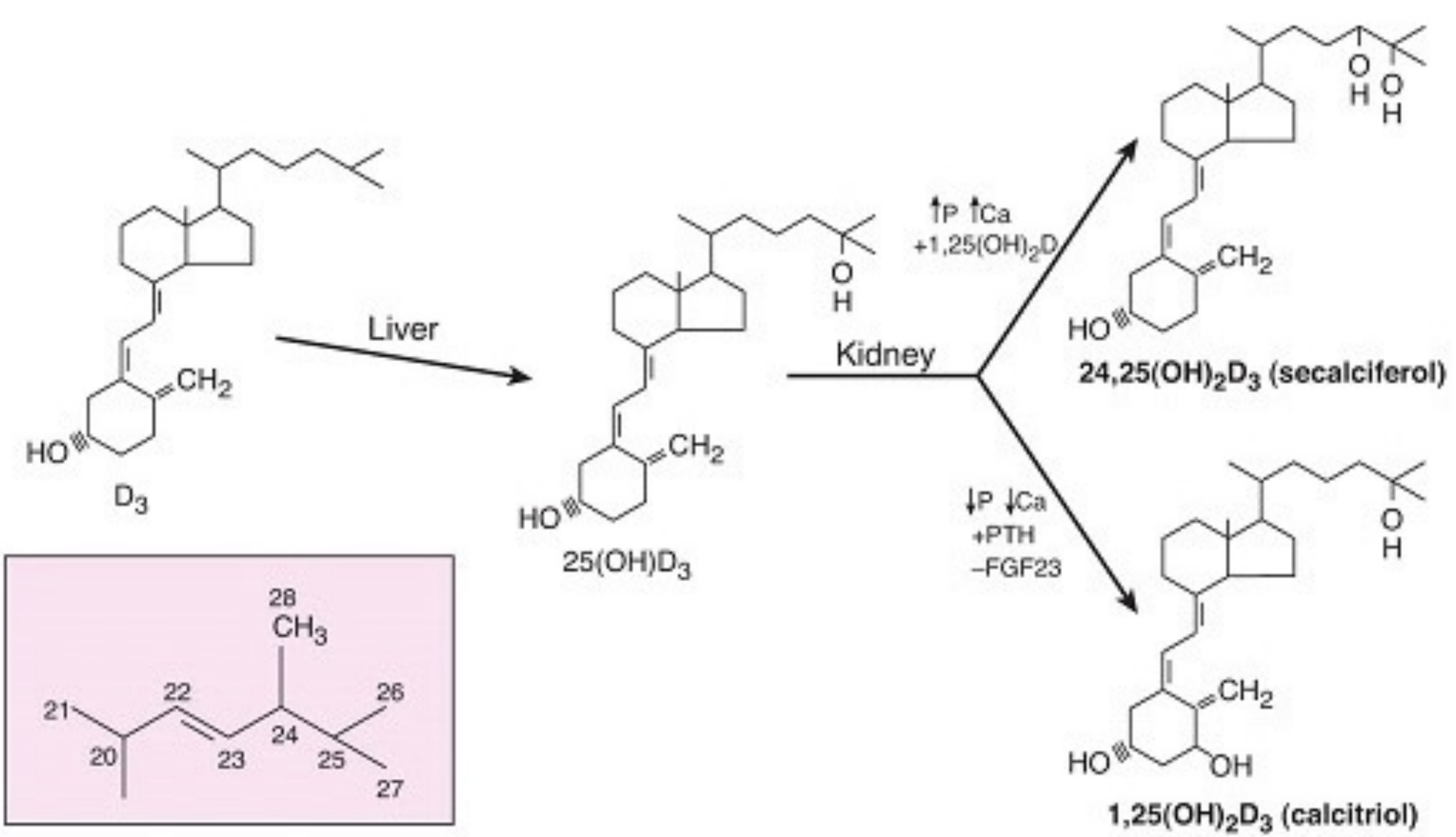
1,25$(OH)_2$ D_3 : Calcitriol ($t_{1/2}$: 1-3 days)


A
1, 25(OH)2D
Gut
Bone
Ca2+
in blood
1, 25(OH)2D
PTH
FGF23
Thyroid
1, 25(OH)2D
Kidney
PTH
Parathyroids
Calcitonin
25(OH)D


B
Monocyte
Stem cells
PTH
1, 25(OH)2D
Preosteoclast
Preosteoblasts
Osteoclast
Osteoblasts
RANKL
MCSF
OPG
Osteoid
Calcified
bone
Bisphosphonates
Calcitonin
Estrogen



7-Dehydrocholesterol
Ultraviolet
Pre D3
Heat
D3 (cholecalciferol)



Liver
Kidney
↑P ↑Ca
+1,25(OH)2D
↓P ↓Ca
+PTH
−FGF23
D3
25(OH)D3
24,25(OH)2D3 (secalciferol)
1,25(OH)2D3 (calcitriol)
HO
CH2
OH
28
CH3
21
22
20
23
24
25
26
27

TABLE 42–1 Vitamin D and its major metabolites and analogs.

Chemical and Generic Names	Abbreviation
Vitamin D_3; cholecalciferol	D_3
Vitamin D_2; ergocalciferol	D_2

TABLE 42–1 **Vitamin D and its major metabolites and analogs.**

Chemical and Generic Names	Abbreviation
25-Hydroxyvitamin D_3; calcifediol	$25(OH)D_3$
1,25-Dihydroxyvitamin D_3; calcitriol	$1,25(OH)_2D_3$

TABLE 42–1 Vitamin D and its major metabolites and analogs.

Chemical and Generic Names	Abbreviation
24,25-Dihydroxyvitamin D_3; secalcifediol	$24,25(OH)_2D_3$
Dihydrotachysterol	DHT
Calcipotriene (calcipotriol)	None
1α-Hydroxyvitamin D_2; doxercalciferol	$1\alpha(OH)D_2$
19-nor-1,25-Dihydroxyvitamin D_2; paricalcitol	$19\text{-nor-}1,25(OH)D_2$

三. Fibroblast Growth factor 23

→FGF 23 是 single-chain protein 有251 amino acids

→它抑制腎臟1, 25 $(OH)_2$ D_3產生及磷再吸收。

(經由sodium phosphate co-transporters Napi2a及2c)

→因此產生 hypophosphatemia 及降低 1, 25 $(OH)_2D_3$在血中濃度。

四、Interaction of PTH , FGF 23 , and vitamin D

1. 1, 25 $(OH)_2$ D→抑制 PTH 分泌
2. chronic kidney disease 因血磷過高→secondary hyperparathyroidism
3. 洗腎病人因血磷高↑

∴要洗腎將血磷降下。

A. 同時服用 1, 25 $(OH)_2$ D_3 (calcitriol)或擬鈣劑 (calcimimetic)抑制副甲狀線增生。

B. 同時服用鈣片(碳酸鈣)，使鈣和磷在腸道結合，而磷不被腸吸收

∴血磷下降

4. calcitriol 也可用於 primary hyperparathyroidism
5. 1, 25 $(OH)_2$ D_3→刺激FGF 23產生↑
6. FGF23→抑制1, 25 $(OH)_2$ D_3 production
7. 但當hypohosphatemia, negative feedback:1, 25 $(OH)_2$ D_3 則抑制 FGF23 production

TABLE 42–2 Actions of parathyroid hormone (PTH), vitamin D, and FGF23 on gut, bone, and kidney.

	PTH	Vitamin D	FGF23
Intestine	Increased calcium and phosphate absorption (by increased $1,25[OH]_2D$ production)	Increased calcium and phosphate absorption by $1,25\ (OH)_2D$	Decreased calcium and phosphate absorption by decreased $1,25(OH)_2$ production
Kidney	Decreased calcium excretion, increased phosphate excretion	Calcium and phosphate excretion may be decreased by 25(OH)D and $1,25(OH)_2D$[1]	Increased phosphate excretion
Bone	Calcium and phosphate resorption increased by high doses. Low doses may increase bone formation.	Increased calcium and phosphate resorption by $1,25(OH)_2D$; bone formation may be increased by $1,25(OH)_2D$ and $24,25(OH)_2D$	Decreased mineralization due to hypophosphatemia
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased	Decreased serum phosphate

[1]Direct effect. Vitamin D often increases urine calcium owing to increased calcium absorption from the intestine and resulting decreased PTH.

■ Secondary Hormonal Regulators of bone Mineral Homeostasis

(1) Calcitonin 抑鈣激素：

使用於Paget's及血鈣過高症

→本品由甲狀腺 Parafolicular cell 分泌，臨床所用者為鮭魚Salmon calcitonin

→本品作用於胃、腎，使血中鈣、磷均↓

→增加礦物質在骨骼中的儲存，抑制破骨細胞的蝕骨作用

∴用於骨質疏鬆

(2) Glucocorticoids :使用於hypercalcemia

cortisol 拮抗 Vit D作用。刺激小腸鈣之 transport由於抑制骨 collagen 之合成 → 造成骨鬆症。

(3) Estrogens :

本品可預防停經後骨鬆症

本品可增加血中1, 25 $(OH)_2$ D 濃度↑

■ Nonhormonal Agents Affecting Bone Mineral Homeostasis

(1) Bisphosphonates : 代表性藥 Etidronate, Zoledronate

- 抑制 1, 25 $(OH)_2$ D 之 production
- 抑制小腸內鈣之transoprt
- 注意：本藥品可能導致非典型股骨骨折 (atypical femur fracture)
- 若感覺大腿或鼠蹊部疼痛,醫師應評估是否為股骨骨折

■ Nonhormonal Agents Affecting Bone Mineral Homeostasis

(2) Mithramycin (Plicamycin)

- 治療血鈣過高症， Paget’s disease (變形性骨炎 Osteitis deformans)

(3) Thiazides :

- 減少腎之鈣排泄
- 減少血鈣過高所引起之結石症

  ∵本品能減少尿中草酸排泄，但能增加尿中鎂、Zinc level ， 此二者能抑制草酸鈣之形成。

■ Nonhormonal Agents Affecting Bone Mineral Homeostasis

(4) Fluoride :

- 可用於鬆骨症新骨之形成
- 防蛀牙dental caries, 水中含 0.5~1 ppm
- 急性中毒：心血管 collapse ， 呼吸衰竭
- 慢性暴露於氟空氣中，會Crippling Fluorosis〔骨贅(椎骨)長骨加粗〕殘廢

(5) Calcimimetics (擬鈣劑) :

- Cinacalcet : 活化 calcium sensing receptor (Ca R)
- 本品 block PTH secretion

→治療 secondary hyperparathyroidism (in chronic kidney disease)

→可降低慢性腎臟病透析患者體內PHT、血清鈣、血清磷, 且可改善骨骼代謝

→治療 parathyroid carcinoma

(6) Strontium Ranelate :

- 本品是由一個 organic ion , ranelic acid 和兩個 strontium 原子所結合
- U.S.A未核准使用，但歐洲使用於osteoporosis
- 本品 block 骨細胞分化。促進 bone formation

II.CLINICAL PHARMACOLOGY

一. Abnormal Serum Calcium & Phospate Levels

1. Hypercalcemia : (除 thiazide 治療之外)

高血鈣症會引起CNS抑制 → coma

主要由於 hyperparathyroidism，骨癌 ; 及次由於 hypervitaminosis D，類肉瘤 Sarcoidosis ，thyrotoxicosis …… 等引起。

【治療】:

(a) 先Saline 補充水分,

再furosemide (diuresis)

(b) Calcitonin-Salmon (Calcimar)

200 MRC unit for inj .

II.CLINICAL PHARMACOLOGY

(c) Mithramycin : 以上藥物無效時，採用之25~50 μg/Kg

(d) Bisphosphonates: zoledronate 4mg infusion

(e) Phosphate : 以上無效時，使用之，緩慢給藥

(f) Glucocorticoids :對於急性血鈣過高，藥效不明，但對於慢性骨癌，可使用之。

(g) Gallium Nitrate: FDA允許使用, 200 mg/m^2 體表面積

II.CLINICAL PHARMACOLOGY

一. Abnormal Serum Calcium & Phospate Levels

2. Hypocalcemia :

- 特徵: 感覺倒錯 (paresthesia)、痙tetany、laryngospasm、muscle cramp、convulsion
- 主要原因係由副甲狀過低症，Vit D 缺乏，腎衰竭，吸收不良malabsorption

低血鈣治療

成人：

(1) Calcium gluconate 0.45 mEq/ml. I.V.

(2) Vit D : 1,25$(OH)_2D_3$(Calcitriol)

每天0.25-1 μg

3.Hyperphosphatemia :

- 腎衰竭之併發症，亦發現於 hypoparathyroidism ，及 Vit D intoxication 。
- 緊急治療用 dialysis , glucose 及 insulin infusion。
  並要限制食物中含磷，及使用 $Al(OH)_3$ gel, 及補充鈣。

4. Hypophosphatemia

- 由下列因素所發生:

  副甲狀過高↑

  Vit D 缺乏

  腎大量排出磷(Fanconi's syndrome) 。

  過量使用 $Al(OH)_3$ gel

- 臨床上少見，肌無力，軟骨病，
- 治療給予 phosphate

  (Fleet phospho-Soda:含816 mg phosphorus / 5 ml;

  751mg Sodium / 5 ml)

二. Specific Disoders Involving The Bone Mineral Regulating Hormones

1. Primary Hyperparathyroidism
   - 外科手術
   - 新的calcimimetic agent (cinacalcet)試驗中
2. Hypoparathyroidism
   - PTH 血鈣↑，血磷↓(正常功能)
   - 血鈣↓，血磷↑(PTH 低者)
   - 給予 Vit D 二萬五~十萬單位每周3次、口服，或給 calcitriol, 或食品calcium supplements

二. Specific Disoders Involving The Bone Mineral Regulating Hormones

3. Nutritional vitamin D defficiency or insufficiency:
   - Rickets 佝僂病或 Osteomalacia 軟骨病
     - 食物中缺 Vit D 或減少陽光
     - 每天給800~1200單位 Vit D
   - 如Vit D defficiency or insufficiency
     - 可用高dose vit D (4000單位/每天)

二. Specific Disoders Involving The Bone Mineral Regulating Hormones

4. Chronic Kidney Disease

→不能製造1,25 $(OH)_2D$

→滯留 phosphate → 會降低鈣離子的濃度

→ Secondary hyperparathyrodism

(因不能製造 1,25 $(OH)_2D$而發生)

鈣在胃腸道吸收↓

∴ 發生Secondary hyperparathyrodism

治療外科切除副甲狀腺parathyroidectomy

5. Intestinal Osteodystrophy 骨發育不全

- 由於胃、肝疾病所造成，為鬆骨症及軟骨病 (osteomalacia)，由於鈣經口吸收不良。
- 使用 calcitriol 。

6. Osteoporosis (骨質疏鬆症)

- 易發生於：停經婦女
  老年人
  長期服用 cortisol , Alcohol abuse ….
- 婦女用 estrogen
- 男人給 Vit D

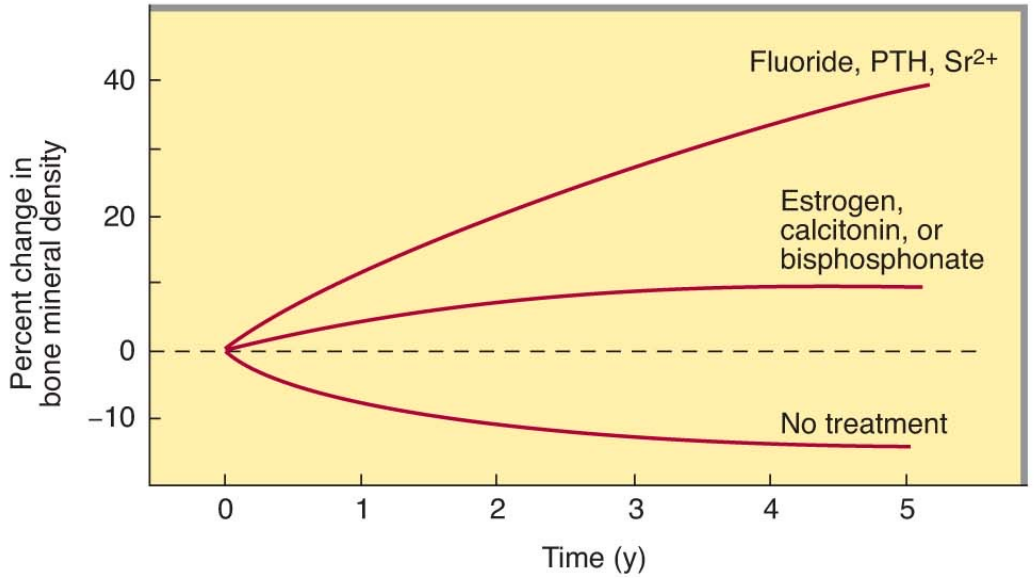


FIGURE 42–5 Typical changes in bone mineral density with time after the onset of menopause, with and without treatment. In the untreated condition, bone is lost during aging in both men and women. Fluoride, strontium (Sr^{2+}), and parathyroid hormone (PTH) promote new bone formation and can increase bone mineral density in subjects who respond to it throughout the period of treatment, although PTH also activates bone resorption. In contrast, estrogen, calcitonin, and bisphosphonates block bone resorption. This leads to a transient increase in bone mineral density because bone formation is not initially decreased. However, with time, both bone formation and bone resorption are decreased with these pure antiresorptive agents, and bone mineral density reaches a new plateau.

7. Vit D – dependent Rickets

(1) Type I

由於CYP27B1突變而缺乏 1,25 $(OH)_2D$ production。

治療用 Vit D 4千單位每天

或 Calcitrol 0.25 – 0.5 μg 每天

(2) Type II

對於1,25 $(OH)_2D$ 之作用無反應，血中之1,25 $(OH)_2D$ 高，

本病少見。

8. Nephrotic Syndrome

- Vit D 是 Prohormone，

  於肝 hydroxylation →25 hydroxy Vit D

  25 (OH)D

  再於腎轉換成 1,25 dihydroxy Vit D

  1,25 $(OH)_2D$

  及24,25-dihydroxy Vit D

  24,25 $(OH)_2D$

- 腎臟疾病症候群的病人是尿中流失Vit D的代謝物→骨疾
- 臨床使用:

  $25(OH)D_3$ Calcifediol

  $1,25\ (OH)_2D_3$ Calcitriol

- α – globulin

  與25(OH)D , 24,25$(OH)_2$D 結合力強

  與Vit D (cholecalciferol)， 1,25 $(OH)_2$D 結合力弱

- Nephrotic syndrome

  喪失 Vit D - binding protein 之能力

  ∴25(OH)D level↓

9. Idiopathic (特發性) Hypercalciuria

(I) 腸過度吸收鈣，使血鈣↑

致PTH ↓

∴ Secondary 增加尿中鈣。

(II) Renal calcium leaker 漏出，使血鈣↓，降低PTH↑

(Ш) Renal phosphate leaker, 病人 primary 減低 phosphate 再吸收使 1,25 $(OH)_2D$ production ↑,

增加腸鈣吸收 ; 使血鈣↑，降低 PTH↓

∴ Secondary 增加 urine calcium

※ 治療可使用 thiazide , 因它之副作用為 hypokalemia, hypomagnesemia, hyperglycemia 及 hypercalcemia。

三、Other Disorders of Bone Mineral Homeostasis

※ Paget's disease of bone

係變形骨炎：

長骨發現腫脹變形，長度不等，而發生步態異常; 顱骨擴大，帽子愈緊 ; 臉痛 ，頭痛 ; high-output cardiac failure 高輸出率的心臟衰竭

【治療】：

(I) 可使用 calcitonin 50~10MRC 單位 s.c.

(British Medical Research Council)

(II) Sod. Etidronate 5 mg/kg/d, 每天P.O.

(bisphosphonates ,抑制 1,25 $(OH)_2D$ 之產生)

※ Enteric Oxaluria

- 病人有脂肪吸收異常 (fat malabsorption) 之 short bowel syndrome

  →可能會有鈣和 oxalate 腎結石

- 此類病人尿中鈣濃度正常或較低，

  但尿中 oxalate 濃度高↑

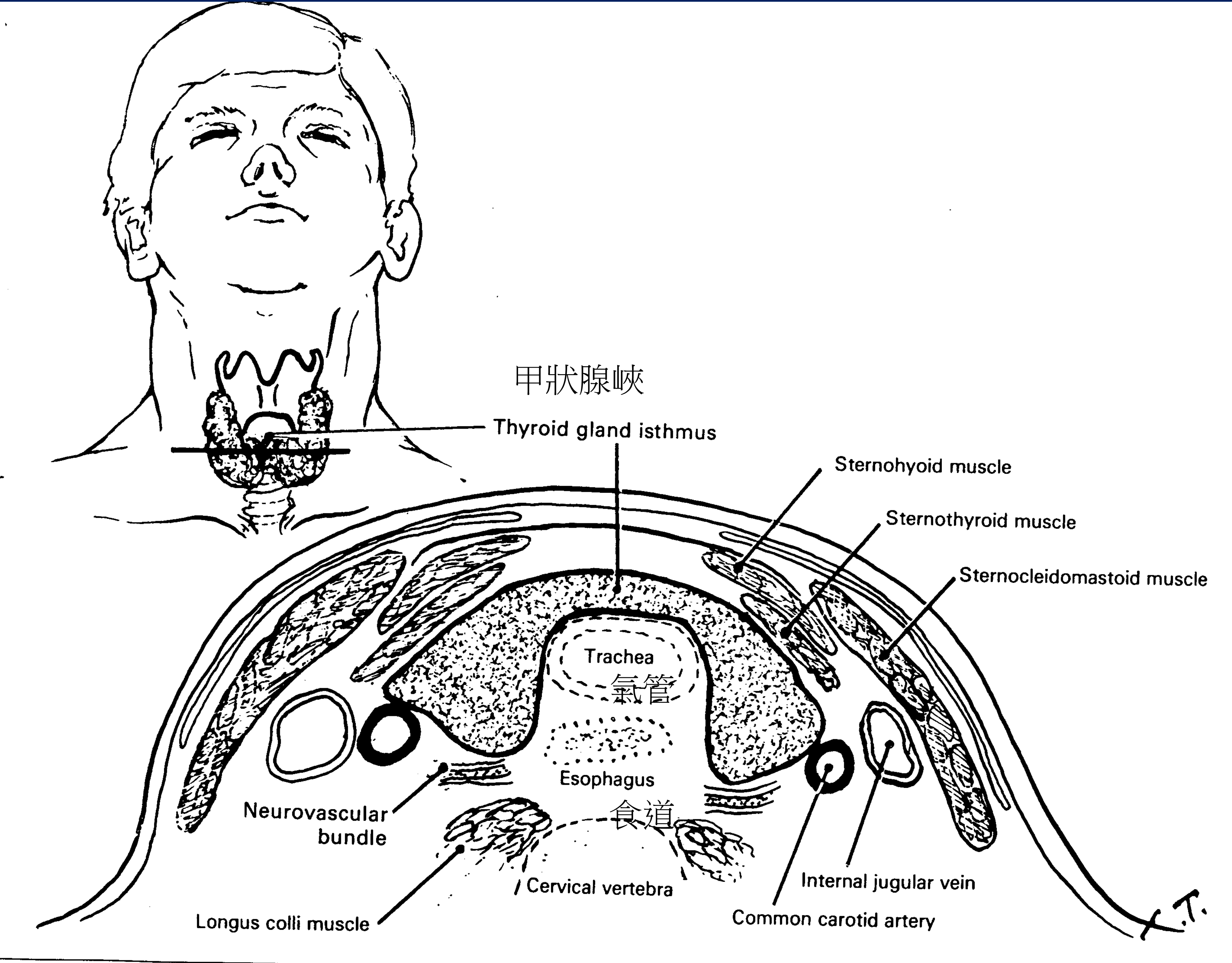
- 每天分開給予 1-2 g calcium carbonate，但要小心監控尿中 oxalate 有下降,但尿中鈣不會增加升高到危險的程度。

尿毒症患者副甲狀腺瘤之治療

陳嘉聖 醫師

中國醫藥學院附設醫院 內科部腎臟科

The Anatomy of Parathyroid Gland



甲狀腺峽
Thyroid gland isthmus
Sternohyoid muscle
Sternothyroid muscle
Sternocleidomastoid muscle
Trachea
氣管
Esophagus
食道
Neurovascular bundle
Longus colli muscle
Cervical vertebra
Internal jugular vein
Common carotid artery

- 副甲狀腺位於頸部甲狀腺的後面，氣管的側面
- 一共有四個，左右分別各兩個
- PTH的功能是維持鈣和磷質在體內的平衡

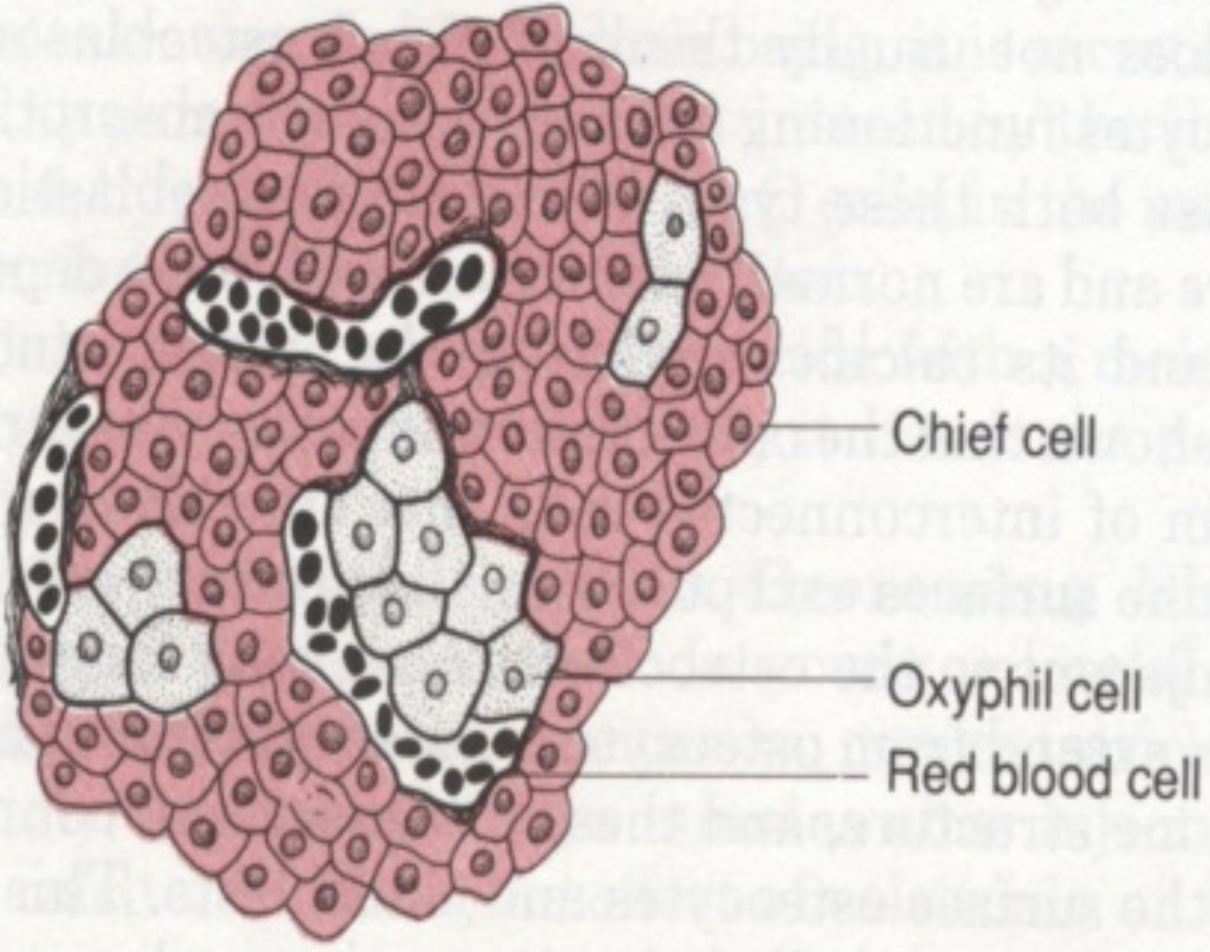


Figure 53–6. Histological structure of a parathyroid gland.

Physiology of Parathyroid Hormone

- PTH is an 84 amino acid polypeptide secreted from the parathyroid glands in response to low levels of ionized Ca in the extra-cellular fluid.
- Increasing circulation of PTH lead to

1. Mobilization of Ca from bone
2. Enhancement of Ca reabsorption in the renal tubule
3. Increased production of $1,25(OH)_2D_3$ by proximal tubule cells

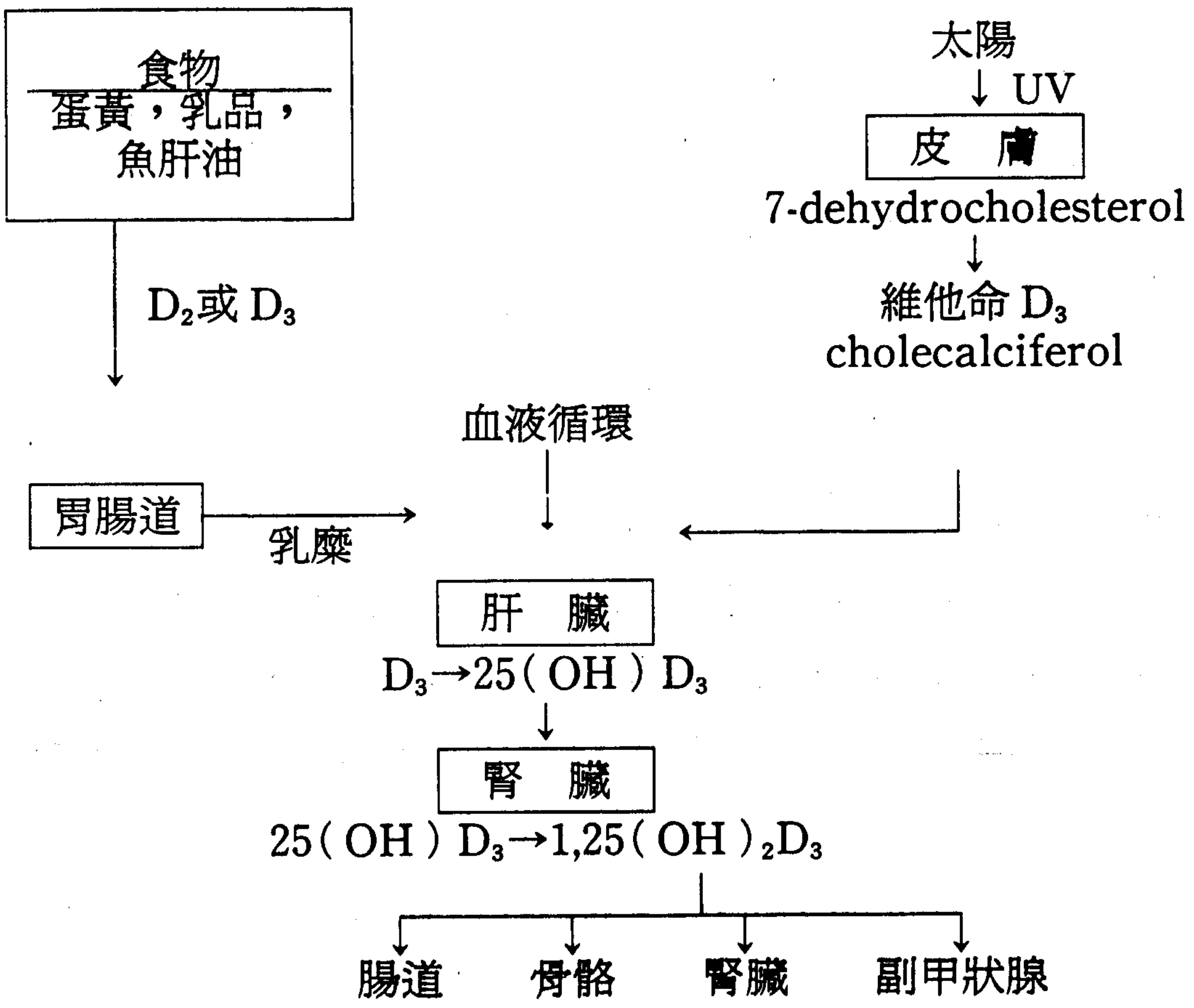
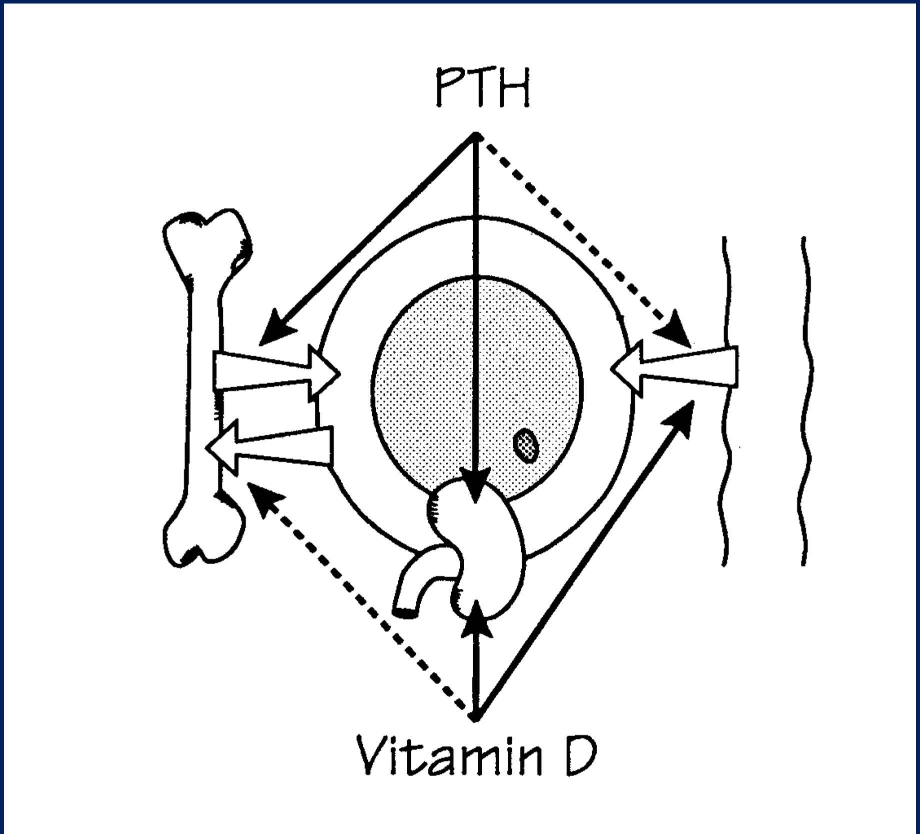


圖27-2維他命 D 之代謝與功能

Normal regulation of Ca & P

bone

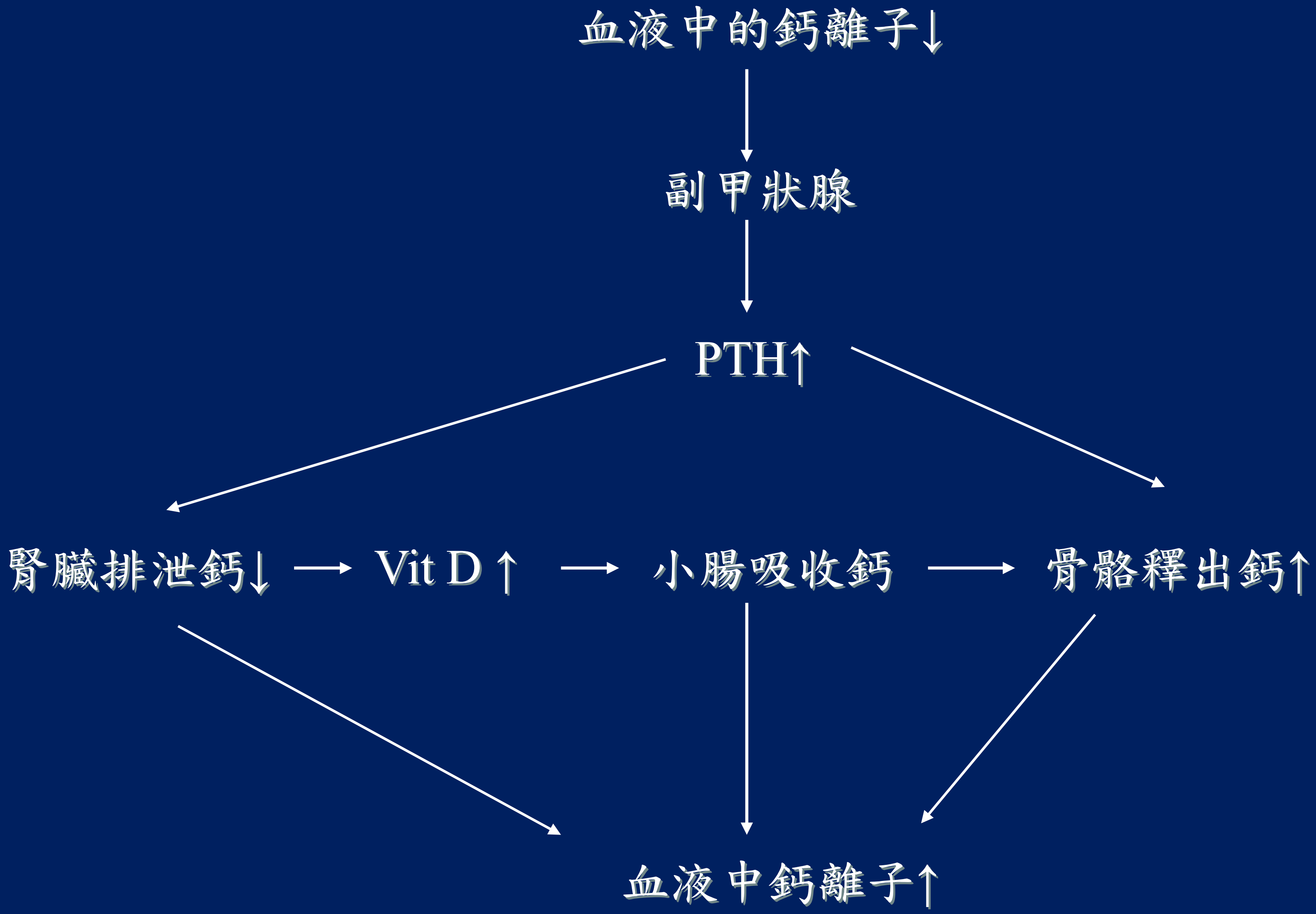


GI tract

- Renal failure→ Ca, P imbalance

The pathogenesis of 2^{nd} hyperparathyroidism (SHP) in uremia

1. Hypocalcemia
2. Phosphate retention—was the most important factor (Salem *Am J Kidney Dis* 1997; 29(6): 862-5)
3. Decreased $1{,}25(OH)_2D_3$
4. Resistance of bone to PTH
5. Abnormal set point of Ca



血液中的鈣離子↓
副甲狀腺
PTH↑
腎臟排泄鈣↓
Vit D ↑
小腸吸收鈣
骨骼釋出鈣↑
血液中鈣離子↑

PTH與鈣

1. 當血液中鈣離子↓, PTH↑
2. 使腎臟減少排泄鈣質
3. 刺激腎臟合成vit D, 來增加小腸對鈣質的吸收
4. 令骨骼增加釋出鈣質
5. 使血液中的鈣離子↑

Secondary hyperparathyroidism (SHPT)

- 主要因磷質高、鈣質低和缺乏vit D
- 在腎功能降低情況下，體內多餘的磷質不能經腎排出

  ∴血中磷質過高
- 過高的磷質，會減少血中的鈣
- 不斷刺激副甲狀腺分泌PTH

  ∴引發副甲狀腺機能亢進

不正常血鈣設定點
Abnormal set point of Ca

一. PTH的分泌是由血鈣濃度所控制

二. ∵慢性腎臟病病人的副甲狀腺的vit D受體及鈣接受器數目減少

∴使鈣質的回饋抑制作用降低。

致造成副甲狀腺對於鈣質的抑制作用敏感度也降低

∴產生了「Abnormal set point of Ca」

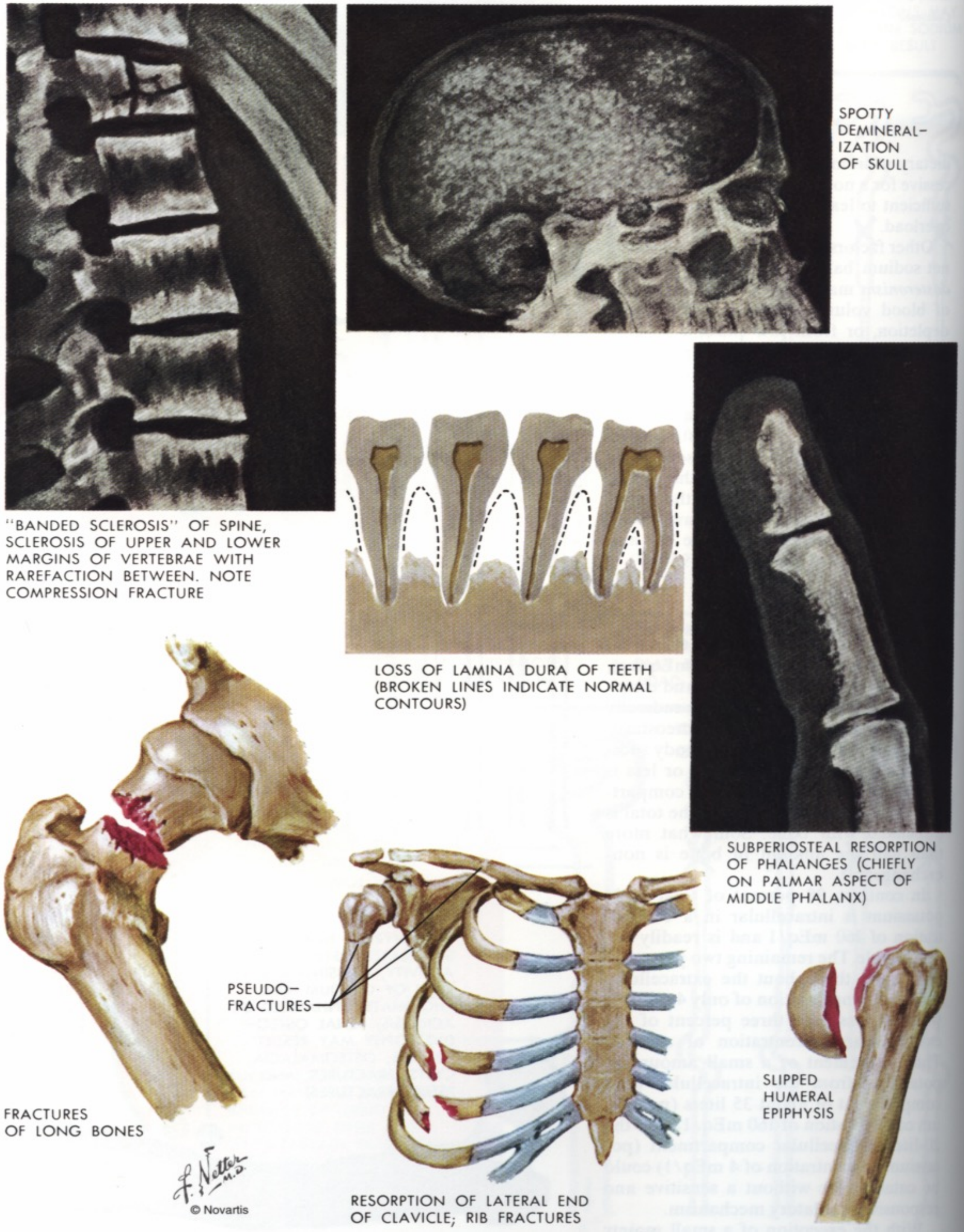
三. 因此需要更高的血鈣值才能抑制PTH的分泌

四. 長期下來，次發性副甲狀腺機能亢進會導致血液中的鈣質過多，骨骼中的鈣質過少

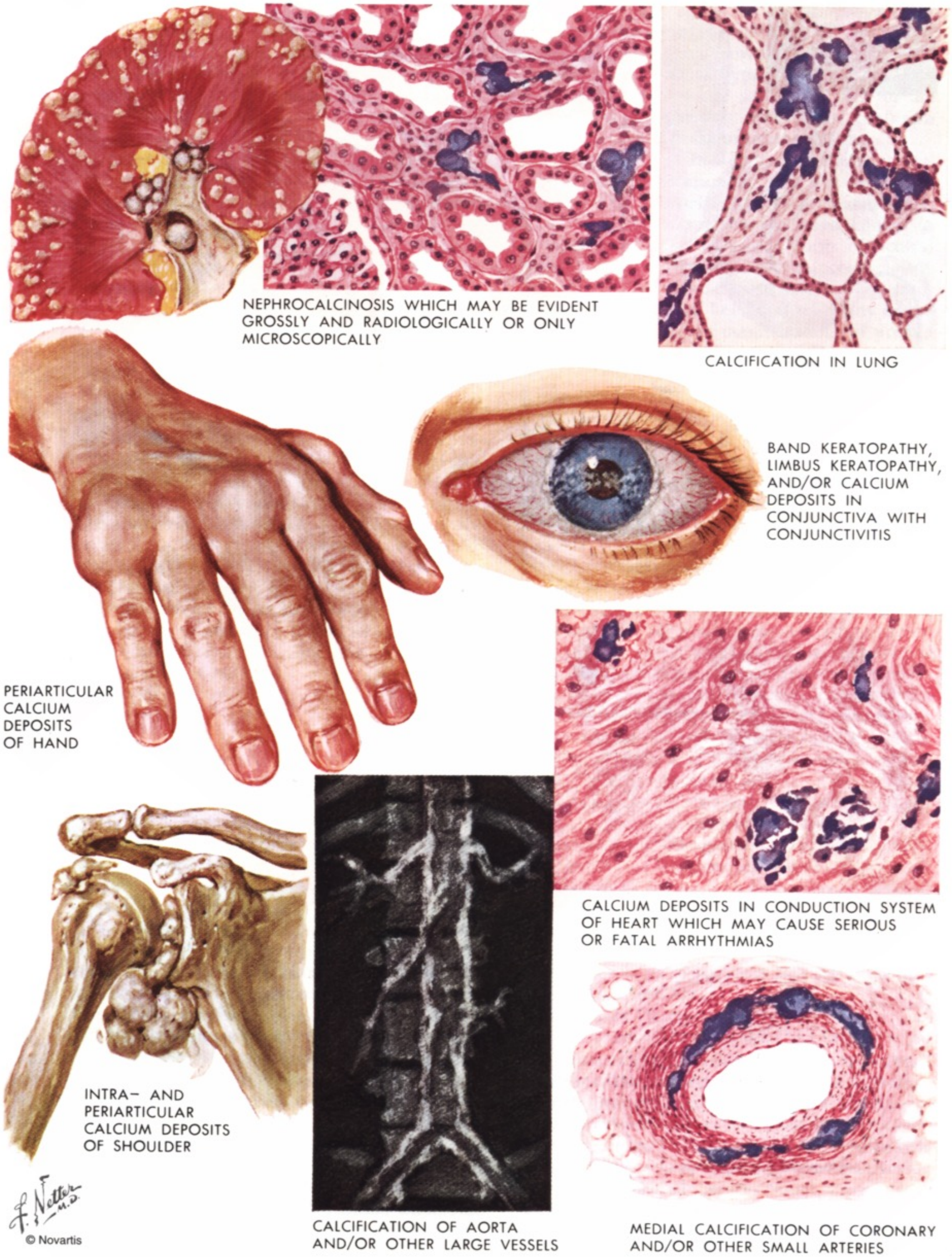
∴會有併發症：

骨質疏鬆、腎結石、心血管疾病。

BONE MANIFESTATIONS OF SECONDARY HYPERPARATHYROIDISM IN CHRONIC RENAL DISEASE



VASCULAR AND SOFT TISSUE CALCIFICATION IN SECONDARY HYPERPARATHYROIDISM OF CHRONIC RENAL DISEASE



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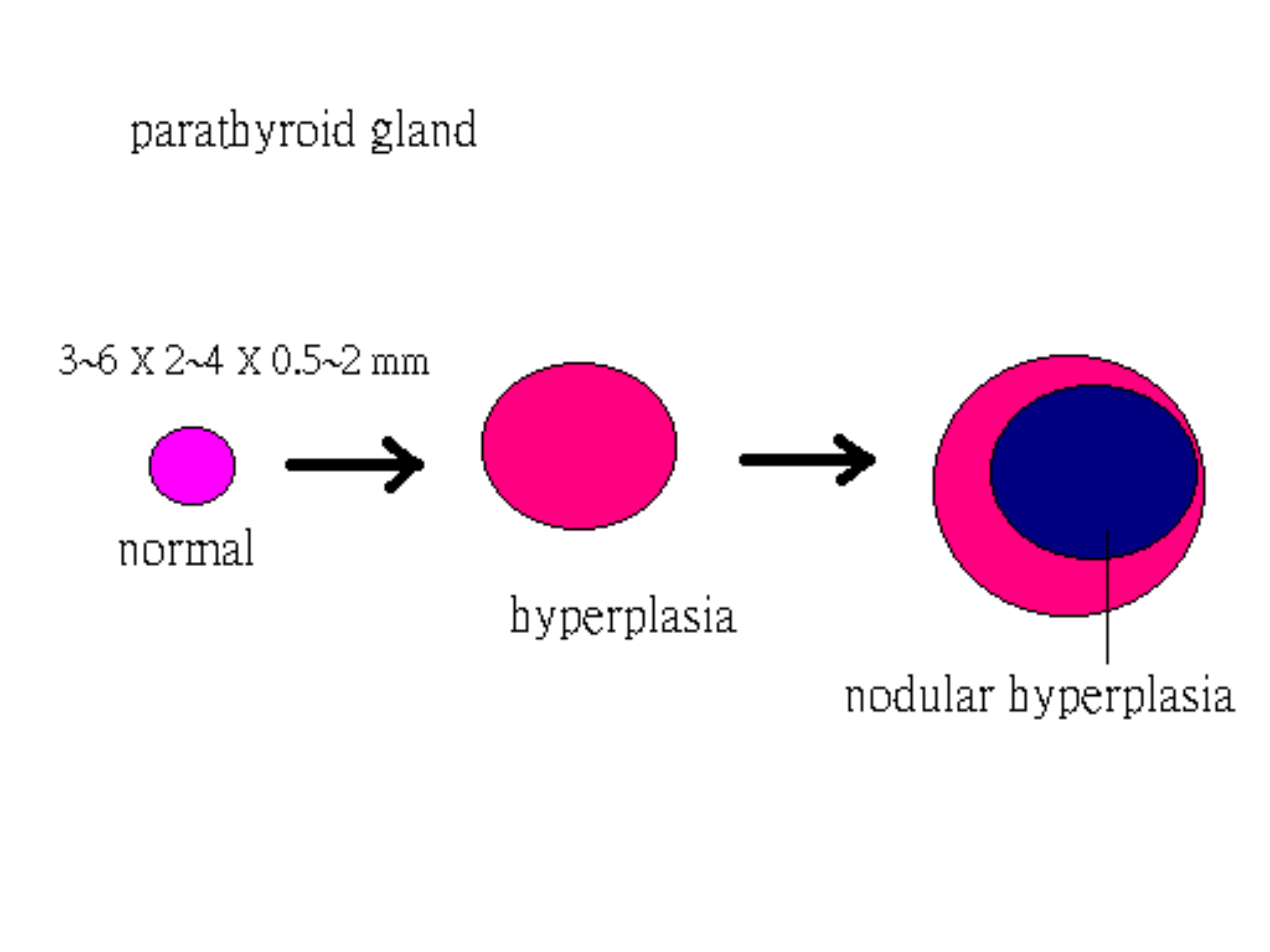
Tx of 2^{nd} hyperparathyroidism

1. Control of serum phosphorus levels (kept 4.5~5.5 mg/dl): $CaCO_3$, $Al(OH)_3$..
2. Prevention of hypocalcemia (kept 9.5~11.0 mg/dl): $CaCO_3$
3. Vitamin D sterol: IV calcitriol, po alfacalcidol

Recent developments in the management of SHP

1. Control serum phosphate: Sevelamer hydrochloride (RenaGelR) 磷結合劑
2. Vitamin D sterol: paricalcitol(降 iPTH, 但比較不會升 Ca, P) : vit D衍生物
3. Calcimimetic agents: modify signal transduction by CaSR (directly activating the CaSR, reduction in PTH release)—R568 (Cinacalcet)

Cell biology of parathyroid hyperplasia in uremia



Surgical procedure of PTX

1. Total parathyroidectomy
2. Subtotal parathyroidectomy (remove 3 parathyroid gland and the 4^{th} remove 75%)
3. Total PTX with autotransplantation

Percutaneous ethanol injection therapy (PEIT)

PEIT 最先由 Italian Solbiati 於1980年代初期提出，後由日本的學者繼續加以發展，並且與內科的療法併用。“選擇性”經皮酒精注射療法，來選擇性的*破壞具“結節型”*增生的副甲狀腺，而*保留“廣泛型"*增生的副甲狀腺，繼續使用內科療法。至1998年6月止，已有超過600名日本病患接受此種治療;經由操作經驗的累積及技術的純熟，已能安全而有效的應用此種治療方法。

PEIT患者的選擇標準

(1)iPTH>400 pg/ml, and Ca level < 10.5 mg/dl。

(2)經影像學檢查，血清學檢查或骨骼切片 (bone biopsy) 證實有 high turn over bone disease.

(3)作超音波檢查，證實有一變大之副甲狀腺，且位於酒精注射針可及之處。

(4)內科治療無效，且排除鋁造成之骨病變(Aluminum bone disease)。

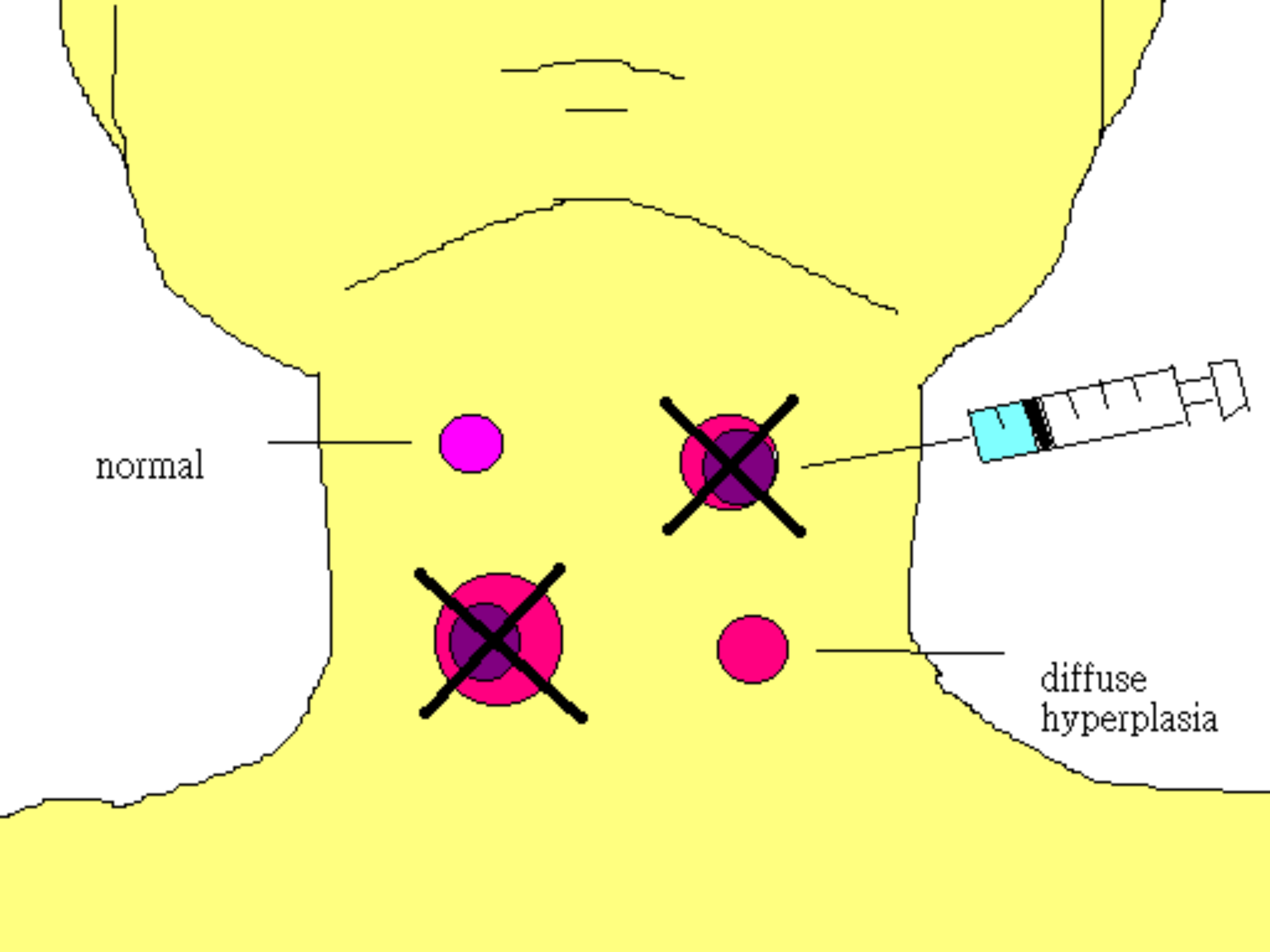
(5)病人的同意。

Procedure of PEIT (1)

1. 首先需要一位對頸部的解剖深入了解並且能熟練操作超音波的專家。
2. 一台7.5 MHZ 或以上，有高解像力(0.5mm)的超音波，具有電子直線形或機械扇形的探頭。此外，Doppler超音波亦是必備的工具，以便確定副甲狀腺是否已被破壞或是有局部復發。
3. 由上述標準選出的病人，其所有直徑大於 lcm 或體積大於 0.5cm 的腺體均接受90%酒精加上1% Lidocaine 的注射治療。

Procedure of PEIT (2)

4. 第一次注射後一個月內需追蹤 iPTH 及使用超音波追蹤是否有殘餘的血流至腺體，若有則需追加少量酒精注射。另外需注意有無出現喉返神經麻痺的現象發生。
5. 酒精注射後同時給予 Vitamin D 的 pulse therapy。若iPTH 降低到治療標準則改為口服 vitamin D 繼續服用。
6. 每月追蹤一次 iPTH，並且每隔數月或於 iPTH上升時追蹤 Doppler echo;若有腺體變大情形，則採用與上述相同的步驟進行治療。


normal
diffuse
hyperplasia